and marked hyalinization of the stroma. The large tumour was a sarcoma of adipose tissue derivation, presenting marked changes in cell shape, size and staining characteristics. Numerous mitotic figures were seen in all fields. This tumour was a liposarcoma type IV.

Follow-up after four and a half years found the patient alive and well, clinically free of recurrent carcinoma or sarcoma.

CONCLUSIONS

Liposarcoma is a rare lesion of the breast. Unlike most sarcomas of the breast, it occasionally metastasizes to the axillary lymph nodes. Metastasis is primarily via the blood stream. When there is no evidence of metastatic spread, and factors in the individual case permit, classical radical mastectomy is the treatment of choice. Radiotherapy, when there is evidence of metastatic disease, may have a palliative effect. Liposarcoma and carcinoma may co-exist within the same breast.

SUMMARY

The literature concerning liposarcoma of the breast is briefly reviewed, and the case of a 76-year-old white woman is presented. The disease is characterized by the presence of a moderately firm, circumscribed mass, freely movable in the surrounding tissues. Often the tumour is present for more than a year before diagnosis is established. Grossly and histologically the picture is similar to liposarcoma elsewhere. It is prone to recur locally and, unlike most sarcomas of the breast, it occasionally metastasizes to the regional lymph nodes. Radical mastectomy is the treatment of choice, provided there is no evidence of distant metastases.

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FREEDOM OF VS. FREEDOM FROM

Freedom of choice means that the person is able to choose his own course of action and his own pattern of living, subject to the requirement that he shall not act so as to violate the freedom of choice of others. Freedom in this sense, it should be noted, is freedom of, not freedom from or freedom to; the preposition is of great importance, for the latter represent not different aspects of the same thing but entirely different conditions. This calls to mind the famous four freedoms enunciated by President Franklin D. Roosevelt during World War II—freedom of speech, of worship, from want, and from fear—later called "a noble pun" by the British economist, Joan Robinson. The two pairs of freedoms were, in fact, of entirely different character. Mr. Roosevelt meant security from want and fear, not freedom or liberty. Many philosophers, including Franklin and Jefferson, have pointed out that freedom and security are inconsistent human conditions. Indeed, make freedom of choice into freedom from choice and one comes close to a definition of slavery.—Editorial, *J. A. M. A.*, 172: 942, 1960.

SHORT COMMUNICATION

THE EFFECT OF NICOTINIC ACID ON HYPERCHOLESTEROLÆMIA*

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NICOTINIC ACID (niacin) amongst many other substances was tested as to its effect in lowering serum cholesterol levels in an effort to inhibit atherosclerosis, but with little or no effect (Jakovleva-Korchagina;[1] Albanese *et al.*[2]). Only when we increased the dose substantially, did we succeed in lowering serum cholesterol in rabbits (Altschul[3]), normal adults, and patients with various diseases (Altschul, Hoffer and Stephen[4]). In addition, development of atherosclerosis in experimental animals was inhibited (Altschul[3]). These findings were confirmed by many other authors, and today nicotinic acid in large doses (minimum 1 g. per 50 lb. body weight) is considered "one of the most uniformly active hypocholesteræmic agents yet studied" (Portman and Stare[5]). In five publications improvement or disappearance of angina pectoris attacks has been reported (Achor *et al.*,[6] Parsons *et al.*,[7] De Soldati *et al.*,[8] Goldner and Vallan,[9] Belle and Halpern[10]). The Council[11] on Drugs of the A.M.A. voted "to expand New and Nonofficial Drugs to describe the use of nicotinic acid in hypercholesteræmia".

The main side effect is cutaneous vasodilatation (flushing and itching), which usually disappears after a few days. In fewer cases, gastro-intestinal reactions occur, which are usually transient, but in some cases they necessitate discontinuing the treatment. This side effect is possibly due to the high acidity of the substance. Therefore Altschul and Hoffer[12] suggested that the pure acid be replaced by a buffered nicotinic acid—at least in patients with gastro-intestinal reaction. Other side effects so far reported (one of thyroid hypofunction,[11] one of jaundice[13]) are not proved to be causally connected with nicotinic acid therapy.

Obviously it is of great interest to establish how the large doses of nicotinic acid lower levels of serum cholesterol. Altschul[14] thought that this effect might be ascribed to increased *in vivo* oxidation, leading to the formation of oxycholesterols which are not atherogenic. Kraupp,[16] by treating animals with heparin and nicotinic acid, found that the cholesterol-lowering effect of nicotinic acid is due to a firmer binding of cholesterol to proteins, thus interfering with the analytical determination of cholesterol, but Sherber and Marcus[17] showed that heparin, added also to

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normal human serum *in vitro*, will increase the yield of cholesterol. Duncan and Best[18] and Perry[19] bring forward the explanation that nicotinic acid decreases hepatic synthesis of cholesterol from acetate; according to Perry, this is due to increased oxidation. Kritchevsky[20] and his associates were able to show that nicotinic acid increases the oxidation of cholesterol by preparations of liver mitochondria.

Friedman and Byers[21] have recently advanced the explanation that the lowering of serum cholesterol by large doses of nicotinic acid in man and animals is due to anorexia. Since it appears to us that the authors have overlooked and misinterpreted the data of other authors, and since at least in two instances their conclusions are based on an error which is easily proved as such, we deem it desirable to comment on their work.

In their series A of rats given 1% nicotinic acid in their feed, the plasma cholesterol level decreased after 12 days by 25%, which the authors term only "a moderate decline". In their controls, the plasma cholesterol level decreased—for no apparent reason—by 7.5%. The first group failed to gain (293 g.: 290 g.), the three grams difference being labelled a loss of weight. This statement applies also to their second experiment, in which, however, according to their Table II the animals gained weight. This is in contrast to the findings by Unna,[24] by Handler and Dann,[25] and by Chen *et al.*[26] who found no inhibition in growth of mice, rats, chickens and dogs given large doses of nicotinic acid or its sodium salt in their food. Only two dogs of Chen *et al.*,[26] given two grams of nicotinic acid daily, died with gastro-intestinal disorders (possibly of distemper?) whereas in Unna's experiments all the dogs tolerated large doses very well.

In series B of Friedman and Byers the rats receiving nicotinic acid for 14 days gained weight (295 g.: 310 g.) although less than the controls (298 g.: 330 g.). The decrease in plasma cholesterol, according to the authors, was slight (−16%), whereas the plasma cholesterol of the controls increased, for no apparent reason, in the same time (+12.2%). If the data on weights given by Friedman and Byers in Table IV are taken at their face value for chi square analysis (for other statistical analysis, the standard errors are missing), it is found that the differences in weight are not significant.

In series D the authors gave 10 rabbits a high cholesterol-oil diet and 10 rabbits the same diet with 0.5% nicotinic acid. Of their first group "only three" (i.e. 30%) died of intercurrent infections; of the second, five (i.e. 50%). The authors consider the difference important and due to the ingestion of nicotinic acid; but a chi square test (with Yates's correction) would have proved to them that the difference in mortality is far from being significant. It appears that their rabbits had an epidemic of "sniffles" with no significant difference ($0.5 > P < 0.95$) in mortality between the group which received nicotinic acid and that which did not. It is, moreover, surprising that a 30% mortality of cholesterol-fed rabbits before the end of the three-month test is considered by the authors as "not unusual". This is certainly not in agreement with the findings of other workers and ourselves. And although the authors state: "Certainly it was our impression that the rabbits fed nicotinic acid, as a group, presented a far less healthy and vigorous appearance than the controls," the rabbits fed nicotinic acid gained as much weight (+46.39%) as the latter (+46.04%) (Table V). The plasma cholesterol level rose to 749 mg. % in the animals receiving cholesterol and nicotinic acid, but to 1020 mg. % in those without nicotinic acid. In view of the small series involved, there is no significance in this apparently considerable difference.

The authors do not accept the weight increase of rabbits fed nicotinic acid in the experiments of Merrill and Lemley-Stone,[25] "because weights of rabbits cannot be employed as an exact indicator of their food intake," thus implying that there was prolonged anorexia in association with gain of weight. In a more recent work, Cava *et al.*[29] found that rabbits receiving 0.5 g. nicotinic acid daily for three months gained 1082 g. in weight, whereas the controls gained only 986 g. The authors seem also to have overlooked Altschul's[3] short-term experiments on rabbits which showed that 24 hours after feeding of nicotinic acid in gelatin capsules the serum cholesterol level was lowered to a highly significant degree. When nicotinic acid was injected subcutaneously, a highly significant fall in serum cholesterol occurred even after four hours. Therefore, anorexia cannot have caused the decrease. Similar "acute" experiments by Kraupp[16] proved significant lowering of serum cholesterol level after administration of nicotinic acid.

As to experience with humans: Friedman and Byers,[21] who report no personal experience, state that weight changes of patients have not been published, admitting, however, that Galbraith *et al.*[28] observed no weight changes in their cases. They overlooked the findings of Achor *et al.*[6] in 16 patients, of whom six gained a combined total of 37 lb., nine lost a combined total of 37 lb. and one had no change, after one year of treatment. They overlooked, further, the report of Gurian and Adlersberg[22] that after the onset of treatment with nicotinic acid "there was an initial gain followed by a subsequent weight loss. It is of interest that the maximum decrease in serum lipids occurred during the period of weight gain." More recently, Parsons and Flinn[23] stressed the absence of significant loss of weight in patients treated with large doses of nicotinic acid. We also wish to contrast the anorexia theory of Friedman and Byers with the statement of Goldner and Vallan:[9] "Many patients indicated that their appetite had increased." Surprising is the criticism of Friedman and Byers of the report by Parsons *et al.*[7] of one case of

TABLE I.—EFFECT OF BUFFERED NICOTINIC ACID (1 G. THRICE DAILY FOR TWO WEEKS) ON WEIGHT AND SERUM CHOLESTEROL IN NORMAL VOLUNTEERS

Case No.	Weight		Serum cholesterol in mg.%*	
	Before	After 2 weeks	Before	After 2 weeks
1	171	171	218	142
2	152	152	178	132
3	170	168	252	235
4	158	158	175	132
5	166.5	168	223	196
6	150	150	198	162
7	167	165	232	188
8	199	197	222	156
9	127	127	162	167
10	72	72	178	135
11	156	153	149	132
12	148	150	230	163
Mean	153	152.5	201.4	161.7

*From Altschul, R. and Hoffer, A.: *Brit.M.J., 2: 713*, 1958.

severe hypercholesteræmia in which the use of nicotinic acid "appeared of doubtful or slight value", which overlooks the other cases reported and also those of Goldner and Vallan,[9] amongst them one of familial hypercholesteræmia in which treatment with nicotinic acid decreased the serum cholesterol level from 1000 mg. % to 250 mg. % in six weeks "in spite of the fact that the fat intake was increased from 30 g. to 60 g. daily".

Finally, we would like to mention the following: in our investigation on the effect of buffered nicotinic acid, the weights of the volunteers were also taken, although not mentioned in the publication. We wish to add here that in the 12 volunteers in which the mean serum cholesterol value decreased by 21.44% from 205 mg. % to 161 mg. % after two weeks of daily medication with three grams of buffered nicotinic acid, the initial mean weight of 153 lb. "decreased" after two weeks to 152.5 lb. (see our Table I). In another, hitherto unpublished series of 17 schizophrenic patients, the mean weight of 151 lb. "decreased" after two weeks to 150.8 lb. after treatment with daily doses of three to six grams of nicotinic acid, whereas the mean serum cholesterol value decreased from 201.4 mg. % to 148.3 mg. % (see our Table II).

TABLE II.—EFFECT OF NICOTINIC ACID (3-6 G. DAILY) ON WEIGHT AND SERUM CHOLESTEROL LEVEL IN SCHIZOPHRENIC PATIENTS

Number	Weight		Serum cholesterol in mg.%	
	Before	After 2 weeks	Before	After 2 weeks
1	152	145	150	130
2	198	186	345	165
3	149	149	185	110
4	161	160	135	145
5	163	161	295	187
6	156	155	260	140
7	132	133	160	125
8	113	116	195	130
9	176	185	195	175
10	95	97	160	130
11	159	160	200	140
12	144	148	175	190
13	124	120	190	155
14	174	173	225	150
15	162	162	185	170
16	126	126	205	175
17	184	188	165	105
T	2568	2564	3425	2522
N	17	17	17	17
Mean	151.0	150.8	201.4	148.3

SUMMARY

The work of Friedman and Byers,[21] leading them to the conclusion that the cholesterol-lowering effect of large doses of nicotinic acid is due to anorexia caused by this medication, is reviewed. It is pointed out that the findings of these authors are not in agreement with the findings of other authors, and that, further, not all of their own findings support their dictum; that some of the pertinent literature has been overlooked and some data have been misinterpreted. More recent reports by other authors and new findings by ourselves also contradict the view of Friedman and Byers.

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